"SYNTHESIS AND CHARACTERIZATION OF NOVEL NITROGEN AND OXYGEN CONTAINING HETEROCYCLES FOR BIOLOGICAL APPLICATION"

Synopsis

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By

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Introduction

1. Heterocyclic compounds

Heterocyclic compounds are a class of cyclic compounds with at least one heteroatom in the ring other than carbon; they are vital to living organisms and play a pivotal role in many biochemical processes and constitute the core in many naturally occurring compounds such as DNA, RNA, NADP, Flavonoids etc. [1,2] Their importance in our day-to-day life has been exemplified by the diverse applications these compounds render, ranging from dyes,[3] sanitisers,[4] resins,[5] tannins,[6] cosmetics, semiconducting devices, to pharmaceutical and agrochemical products.[7]

While a variety of heterocyclic compounds could be accessed with modern synthetic methodologies, the most frequented heterocycles include five and six-membered heterocycles, containing predominantly at least one nitrogen (N) or/and oxygen (O) as hetero atom such as pyrrole, isoxazole, furan, imidazole, pyridine, Pyrazine, coumarins, isoxazolines, pyrimidines, benzoxazoles, quinolines (**Figure 1**).[8]

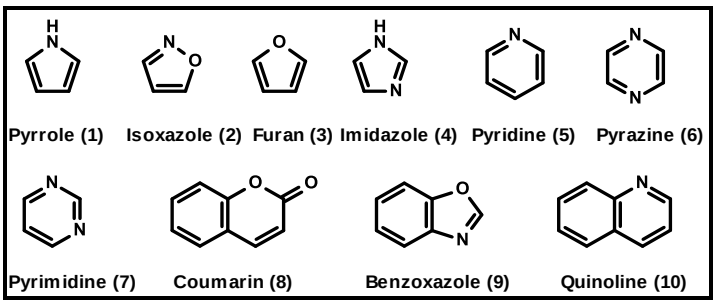


Figure 1: Few simple and fused nitrogen and oxygen-containing Heterocyclic compounds

Recent trends in the literature indicate that the properties of the heterocyclic compounds can be modulated by the introduction of fluorine atoms,[9] because of its exclusive properties such as small size (bio-isostere of hydrogen atom[10]), lipophilicity, electronic properties, and rendering metabolic stability. Thus, fluorine-containing heterocycles are increasingly being investigated for small molecule active ingredients and continue to inspire discovery programs including libraries (**Figure 2**) both in industry and academia. [11,12]

Accessing heterocycles with diverse substitution pattern pose synthetic challenges due to structural complexity and substitution pattern hence, demand methodology development. Traditional approaches include a linear synthetic methodology, convergent synthesis,[13] click chemistry,[14] multi-component reactions,[15] heterocycle-heterocycle interconversion,[16] combinatorial methodologies,[17] and diversity-oriented synthetic approach.[18]

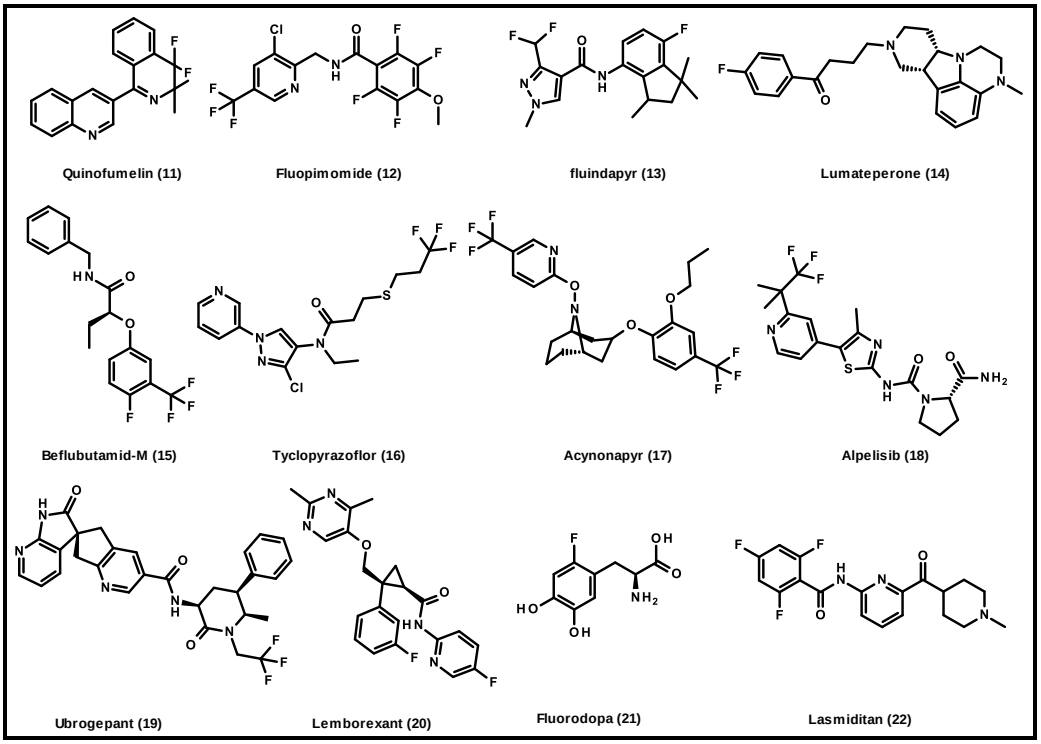


Figure 2:Fluorine containing Biologically active molecules in the market.

Among the several existing approaches,[19] diversity-oriented synthesis (DOS) is being increasingly explored methodology for synthesizing complex heterocycles as they offer structural diversity and complexity efficiently, allowing access to large collections of libraries.[20] The success of the approach has been due to the use of versatile scaffolds, such as aminozoles,[21] carbonyl compounds,[22] α,β unsaturated carbonyls, triazolo[1,5-a][1,4]diazepines,[23] sp^3-rich morpholine peptidomimetics,[24] pyridines[25] etc. Among these scaffolds, the use of α,β unsaturated carbonyl compounds is very well investigated in the synthesis of heterocycles.[26] However, to our surprise, there are limited reports available for the synthesis of scaffolds like cyclic enones and enediones, especially the enediones with di-substitution in the β-position. In 2009, V. V. Dabolkar *et. al.*, reported the synthesis of fused isoxazole and pyrazole derivatives using cyclic-enediones, albeit on a mono-substitution at the β-position. Interestingly, they found the isoxazole and pyrazole derivatives to have anti-microbial property.[27] To our surprise, there were no reports on enediones with di-substitution in the β-position, especially with a trifluoromethyl group at the β-position as a substituent. Thus, we undertook the opportunity to explore the area and demonstrate the synthesis and synthetic utility of these intermediates to access complex heterocycles for application in agrochemical research *via* the reagent-based diversity-oriented synthetic approach.

Mono and di-quaternary salts of heterocyclic compounds such as imidazole, pyridines and their derivatives have been of interest for various applications, including ionic liquids,[28] agrochemicals,[29] and material science.[30] Presence of a mono or di-charge render special

physical properties such as high vapour pressure, and high boiling point, and enhance oxidizing power of the compounds. The di-methylated quaternary salt of 4,4'-bipyridine has been widely applied in the past as an herbicide (paraquat), popularly known as viologen.[31] Attempts, in the past, had been made to prepare diquaternary salts of pyrazinium slats for their application as electroactive surfactants and due to their enhanced reactivity (high charge to surface area compared to paraquat), they were found stable only in acidic conditions. To circumvent the challenges posed by di-charge, it was envisioned that directed hydrogen-bonding on mono-charged pyrazinium salts might render similar properties of di-quaternary salts of pyrazine albeit with lower oxidizing power, however, might enhance stability. In the current work, a diversity-oriented strategy was evolved to prepare mono-charged pyrazinium salts with a hydrogen bond donor attached to the molecule.

Thus, the current thesis work exemplifies the use of reagent-based diversity-oriented synthesis to synthesize an array of molecules that are important in crop-protection research. Using this approach, the following two areas of research are taken into consideration for the work:

i) Synthesis of the fluorinated α,β-unsaturated carbonyl compounds and their use in the preparation of heterocyclic compounds for biological application.
ii) Synthesis of different pyridinium- and Pyrazinium- charged species using different alkyl and alkoxy halides for biological application.

1.1 Objective of the research.

1. To apply diversity-oriented synthesis to access complex and diverse heterocycles for agrochemical application.
2. To enhance the molecular solubility and lipophilicity of the molecule by incorporating trifluoromethyl group.
3. Synthesis of scaffolds that can be excellent precursors for the synthesis of different 5- and 6- membered heterocyclic compounds targeting agrochemical application.
4. Synthesis of mono-charged pyridinium and pyrazinium salts and their application in agrochemical activity.

Chapter 1: Introduction

This chapter introduces the following area of research,

1. Synthesis of trifluoromethylated cyclic-enediones.
    a. Literature on fluorinated/ trifluoromethylated biological active compounds.
    b. Significance of fluorinated/ trifluoromethylated compounds in biological active compounds.

2. Synthesis of five and six-membered fused heterocyclic compounds using trifluoromethylated enediones.
    a. Literature on the synthesis of trifluoromethylated five and six-membered fused heterocyclic compounds.
    b. Application of trifluoromethylated five and six-membered fused heterocyclic compounds in medicinal and agrochemical fields.
3. Synthesis of mono-charged pyrazinium and pyridinium salts.
    a. Literature on the synthesis of mono-charged pyrazinium and pyridinium salts.
    b. Application of mono-charged pyrazinium and pyridinium salts.

A brief description of their synthesis, application and biological activity has been discussed based on publications appearing in chemical literature up to 2021.

2. Chapter 2: Synthesis of Novel trifluoromethylated cyclic-enediones

α, β-Unsaturated carbonyl compounds are amongst the most fundamentally important functional compounds and are extensively applied in medicinal chemistry, synthetic chemistry, material chemistry and crop-protection research.[32,33]

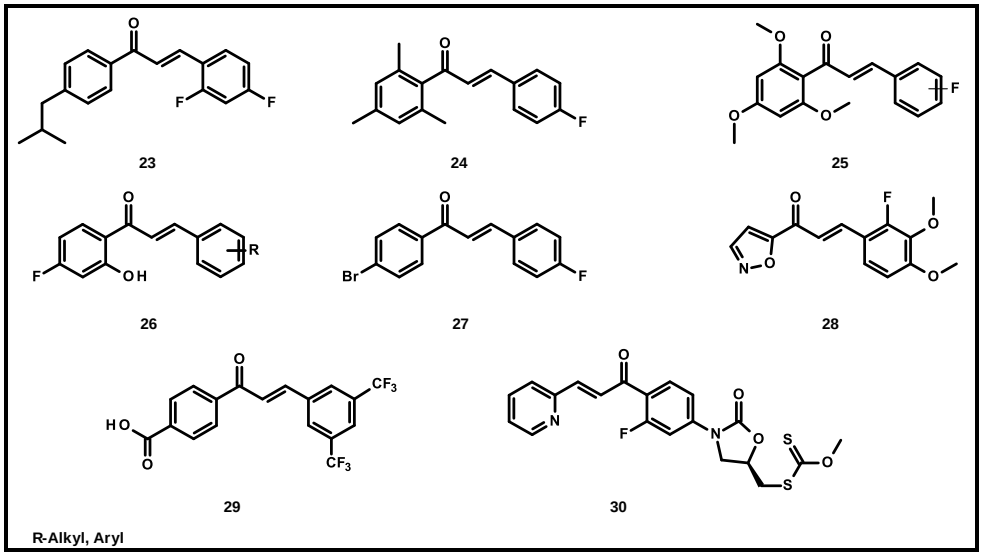


Figure 3: Structures of fluorinated chalcones with antibacterial and antifungal activities

Among them, fluorinated *α, β*-unsaturated carbonyl compounds/chalcones possess exciting biological activities[34,35] (**Figure 3**) and are also excellent precursor for a variety of heterocycles hence, the synthesis of these compounds could pave the way of novel heterocycles with significant biological activity. Hence, in this chapter, we attempted to access the cyclic-enediones with di-substitution at the *β*-position and demonstrated their synthesis for the first time and evaluated their application to novel heterocycles in chapter-3 and 4.

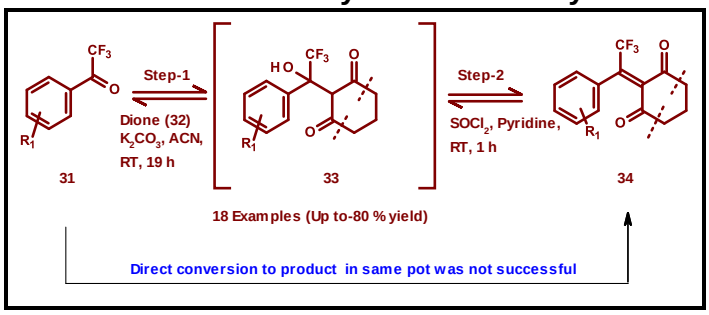
Traditionally, the enediones could be obtained *via* the classical condensation methods, including Aldol, Claisen–Schmidt, Knoevenagel condensations, etc.[36] But surprisingly, there were no reports available in the literature for tetrasubstituted cyclic-enediones with a CF_3 group. We hypothesized that the target compound can be accesses *via* condensation of a trifluoromethyl aryl ketone with a cyclic 1,3 dione. The chapter describes the optimisation of parameters to access the title compounds, scope and general utility of the methodology, stability, characterisation of the compounds and their biological activity.

2.1 Current work

2.1.1 Optimisation.

To test the hypothesis, 1, 3-cyclohexadione and Aryl CF_3-ketone are taken as model substrates, and the reaction was carried out with different solvents and bases, as summarized in above **Table 1**.

Table 1: Optimization of tetrasubstituted cyclic-enedione synthesis



Entry No	Base or Reagent	Solvent	Conversion to 33 (%) *
1	K_2CO_3	Toluene	Traces
2		THF	32
3		NMP	62
4		**Acetonitrile**	**84**
5		Methanol	2
6		Water	0
7	Pyridine	Acetonitrile	6
8	DABCO		18
9	TEA		36
10	Piperidine		28
11	DBU		60
12	BF_3Et_2O (1.7 equiv.)	DCM	0
13	NaOH	Methanol	0
14	-	Water	0

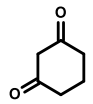
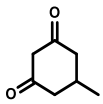
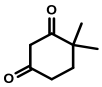
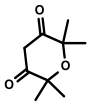
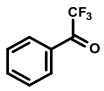
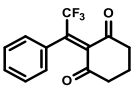
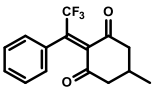
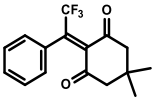
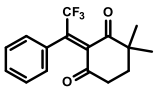
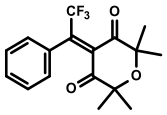
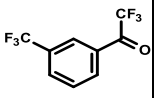
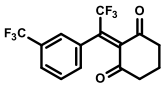
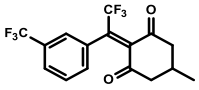
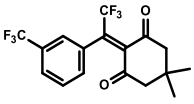
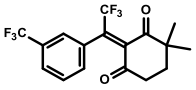
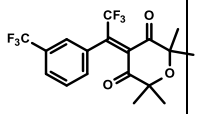
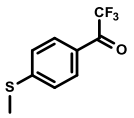
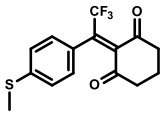
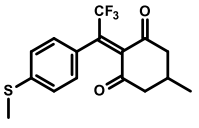
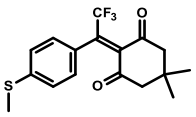
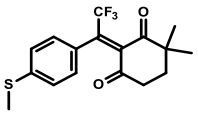
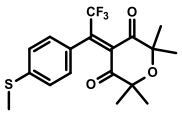
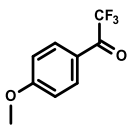
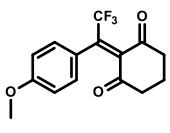
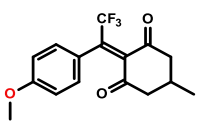
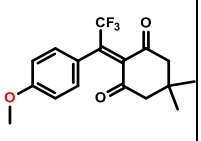
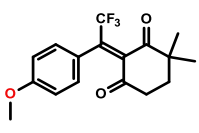
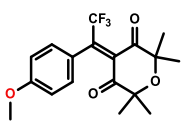
* After 19 h of reaction time at RT

Among the different solvents used, acetonitrile and NMP gave good conversion of starting material to Michael adduct **33**. From the above results, acetonitrile was identified as the choice of solvent, and to further optimize the reaction conditions screening experiments with various bases were carried out (**Table 1, Entry-7 to entry-11**), and potassium carbonate was found to give the best conversion among all other bases used. However, isolation of **33** were not successful; water workup in all the cases gave traces to the poor yield of the crude adduct **33** due to the retro-aldol reaction occurring, leading to the formation of starting materials. Attempts made for direct conversion to product **34** from **31** were unsuccessful (**Table 1, Entry 13-14**). Reactions containing **33** prepared from organic bases when concentrated and treated with thionyl chloride followed by pyridine at room temperature gave **34**, albeit in poor yields. when crude **33** obtained from entry-4 (**Table 1**) after filtration of the reaction mixture through celite, concentrated and followed by treatment with thionyl chloride, pyridine gave crude **34,** which upon column chromatography furnished moderate yield of 52% at room temperature with toluene as solvent.[37]

2.2 Substrate the scope of the methodology.

The condensation yields were found to be in reasonable to good yields when symmetrical cyclohexane-1,3-diones are condensation partners (30–80%, symmetrical enolate formation).

Table 2: Summary table depicting the synthesis of β,β-disubstituted-1,3-dicarbonyl compounds (34a-t) synthesised over two steps from cyclohexane-1,3-dione (32a-e) and trifluoroacetophenone (31a-d).

	 32a (*p*Ka: 5.26 ±0.20)	 32b (*p*Ka: 5.29 ±0.20)	32c (*p*Ka: 5.32 ±0.40)	 32d (*p*Ka: 5.33 ±0.40)	 32e (*p*Ka: 9.38 ±0.60)
 31a (GB: 0)	 34a (52%)	 34b (50%)	 34c (65%)	 34d (17%)	 34e (55%)
 31b (GB: -5.8)[12]	 34f (57%)	 34g (51%)	 34h (73%)	 34i (18%)	 34j (41%)
 31c (GB: 10)	 34k (21 %)	 34l (43%)	 34m (80%)	 34n (49%)	 34o (69 %)
 31d (GB: 10.9)	 34p (traces)	 34q (31%)	 34r (21%)	 34s (10%)	 34t (traces)

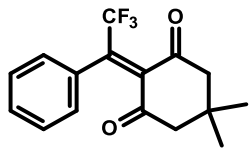
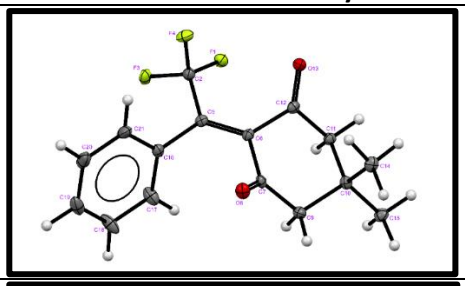
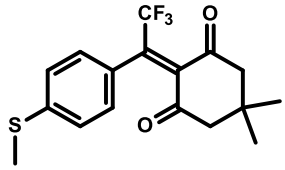
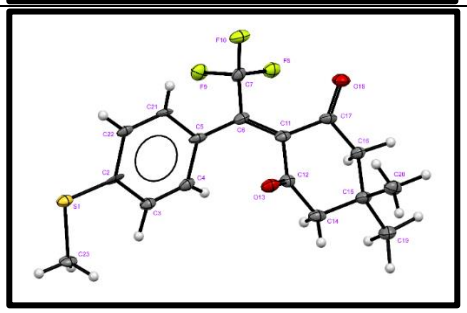
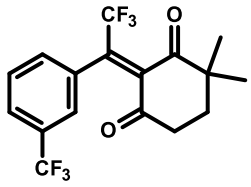
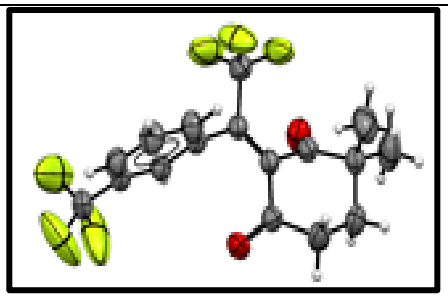
The yields were found to be very low when unsymmetrical enolate formation was possible ex. **32d** as starting material (10–49%). No product formation to poor yields were obtained for the

condensation product where trifluoroacetophenone with electron donating group (**31d**) was used by one of the partners. This could be due to reduced electrophilicity of the carbonyl carbon as a result of resonance stabilization of the p-methoxy group on the ring.

2.3 Structure confirmation by X-ray analysis.

Tetra-substituted β-trifluoromethyl cyclohexane- α,β-enediones **34a, 34d** and **34n** were further characterized by X-ray crystallography (**Table 3**). The crystal structure indicates that

Table 3: X-ray crystallography of **34a, 34d, 34n**.

Molecule	X-ray
 **34a**	
 **34d**	
 **34n**	

the crystals of **34a** and **34d** contain an equal ratio of two mirror-image conformations, and that the cyclohexane dione ring exists only in the chair conformation. Whereas **34n** was found in both *E* and *Z* forms.

2.4 Biology.

All the molecules synthesised were tested for biological activity in all three indications (i.e., insecticide, fungicide, and herbicide) of agrochemical interest.

1. Molecules showed poor to mild activity in fungicide indication.
2. Trifluoromethylated cyclic-enediones with *S*-methyl in the aromatic ring showed moderate fungicidal activity among all the products tested.

2.5 Summary and Conclusion.

The major finding of this chapter based on synthetic utility and biological evolution are as follows:

1. A new and scalable methodology for the synthesis of trifluoromethylated cyclic-enediones has been developed.
2. The structure of the compound was confirmed based on ^{1}H NMR, 2D NMR spectra, and HRMS and confirmed by X-ray analysis.
3. The compounds have been tested in the agrochemical field to test their potential as fungicides, insecticides, and herbicides. The compounds did show mild fungicidal activity and no significant level of activity in other area, i.e., Herbicidal and insecticidal.

3. Chapter 3: Application of trifluoromethylated cyclic-enediones in the synthesis of 6-membered heterocycles.

6-membered heterocyclic compounds are derived from the replacement of at least one carbon atom of benzene by an iso-electronic atom. 6-membered heterocyclic compounds are further subdivided into the following categories.

1. Heterocyclic compounds with a single hetero atom.

2. Heterocyclic compounds with multiple hetero atoms.

3. Fused or condensed heterocyclic compounds

Many of the biologically important 6-membered heterocycles can be broadly partitioned into the following sections, categorized by analogous groupings of heterocyclic rings.[38,39,40]

1. Pyrimidines and quinazolines.
2. Pyrans and dihydropyrans. [41]
3. Pyridines and quinolones.
4. Pyrazines and piperazines.
5. Pyridazines and perhydropyridazines.
6. Dihydropyridines and piperidines.
7. Triazines and polyazacyclic systems.

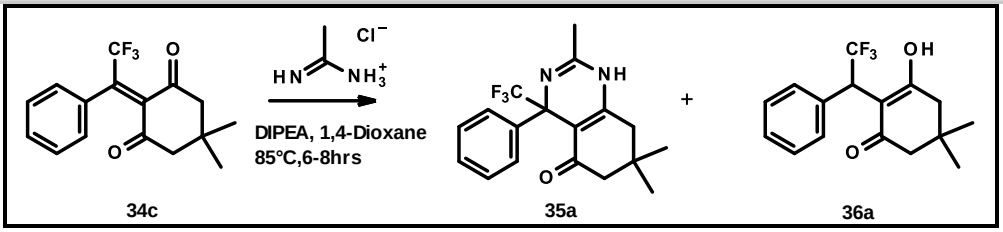
Here in, we report the synthesis of novel trifluromethylated fused pyrimidines, and 4*H*-pyrans from cyclic enediones using amidinehydrochlorides and malononitrile, respectively.

3.1 Current work

3.1.1 Synthesis of 1,4-dihydropyrimidines.

Our exploration of the synthesis of 1,4-dihydropyrimidines initiated by a reacting **34c** with ethanimidoylammonium;chloride, and the results were summarized in **Table-1**.

Table 4: Optimisation of reaction conditions for accessing **35a** *via* reaction between **34c** and ethanimidoylammonium;chloride.



Entry	Base (2 equiv.)	Conditions °C/ Time h	Solvent	Conversion by HPLC 35a/36a (%)
1	TEA	reflux/36	THF	40/30
2	DIPEA	reflux/36	THF	55 [a]/2
3	DIPA	reflux /36	THF	59/-
4[b]	DIPA	85/6	1,4-Dioxane	88[a]/-
5	DIPA	100-101/5	1,4-Dioxane	75/-

[a] Isolated yield, [b] Optimized condition-1

Initially, the reaction was carried out in THF with triethylamine as a base, to our delight, desired product **35a** was obtained along with an impurity at reflux in 36 h. Upon isolation and characterisation of the impurity, it indicated the formation reduced **34c** to give **36a (Table 4, Entry 3)**. When Triethylamine was replaced with other organic bases, such as DIPEA, traces of **36a** was observed along with product **35a (Table 4, Entry 4);** however, when DIPA was used, only the desired product **35a** was obtained **(Table 4, Entry 5)**. Changing the reaction solvent from THF to 1,4-dioxane and heating the reaction mixture at 85 °C gave **35a** in 88% yield **(Table 4, Entry 6)**. Carrying out the reaction at reflux dioxane had conversion completed within 5 h, however, with at least 10–13 % lower yield **(Table 4, Entry 7)**.

With this optimized condition in hand, we studied the substrate scope of the reaction. Trends in the yields of the reaction is as summarized in **Figure 4.** Different imidoyl ammonium chlorides were reacted with trifluoromethylated cyclic-enediones (**34**) using optimized conditions to give the products in moderate to excellent yields.

When ethanimidoylammonium chloride was treated with simple enediones, good to excellent yields were obtained for **35a** (88%), **35b** (86%) and **35c** (70%). Interestingly, with enedione containing *S*-methyl at the aromatic ring gave a moderate yield of 64% **35d**. Upon reaction of benzenecarboximidoyl ammonium chloride with trifluoromethylated cyclic-enediones (**34**)

gave good to excellent yields **38a** (77%), **38b** (75%), **38c** (72%), **38d** (70%), **38e** (70%) and **38f** (70%).

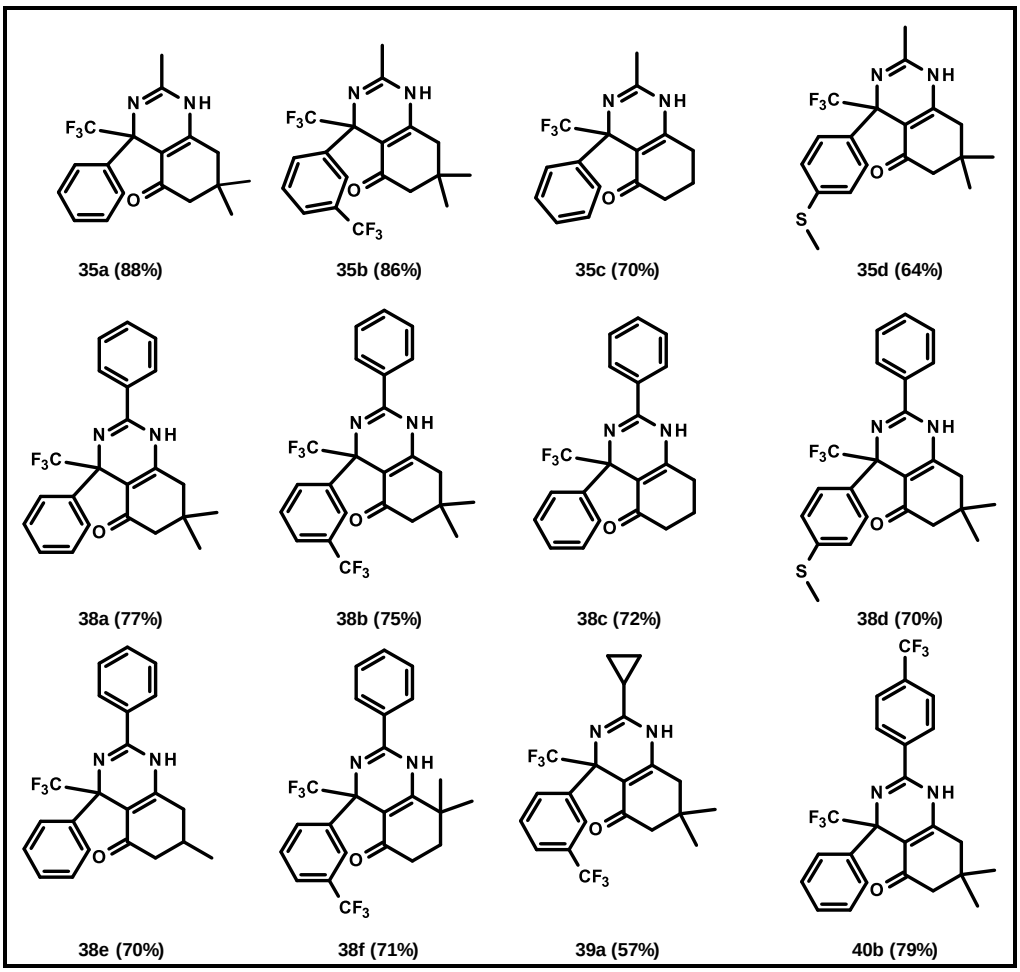
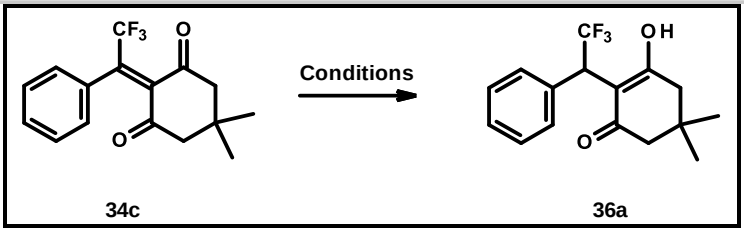


Figure 4: Substrate tolerance for synthesis of Fused pyrimidine derivatives

3.1.1 Reaction of triethylamine with trifluoromethylated cyclic-enediones.

Earlier, during the synthesis of fused 1,4-pyrimidines using trifluoromethylated cyclic-enediones (**34**) and aminoimdines with triethylamine as a base **(Table-4, entry-3)**, we observed an impurity **36a** along with desired product, which upon characterisation found to be reduced starting material, i.e., reduced cyclic enedione. Upon investigation, it is found that triethylamine was responsible for this reduction. The impurity isolated in the reaction was C-alkylated 1,3-dione. Usually, the alkylation of 1,3-diones gives an O-alkylated product as a component. Therefore, we decided to further optimised the condition to prepare exclusively the C-alkylated 1,3-dione by treating 5,5-dimethyl-2-(2,2,2-trifluoro-1-phenyl-ethylidene) cyclohexane-1,3-dione with an excess of triethylamine in 1,4 dioxane as a solvent and could able to isolate 60% yield.

Table 5: Optimisation of reaction conditions for accessing 3**6a** *via* reaction between 3**4c** and triethylamine.



34c 36a

Entry	Temp, °C	Base (equiv.)	Time h	Solvent	Conversion (By HPLC) 34c/36a in %
1	85	Et_3N (3)	24	1,4-Dioxane	17/58
2	85	Et_3N (5)	5	1,4-Dioxane	17/57
3	100-101	Et_3N (5)	5	1,4-Dioxane	-/70(60[a])
4	100-101	DIPEA (5)	24	1,4-Dioxane	98/2
5	100-101	DIPA (5)	24	1,4-Dioxane	100/-

[a]Isolated yield

Initially, reaction was done using 3 equiv. of triethylamine in 1,4-Dioxane at 85°C for 24h **(Table 5, Entry-1)**, expected product **36a** was formed in 58% by HPLC analysis with 17% starting material intact. When the triethylamine quantity was increased to 5 equiv., reaction completed in 24h. Further, the reaction of **34c** and triethylamine (5equiv.) was carried at reflux temperature, resulted in a full conversion of **34c** to give 70% of **36a** in 5h **(Table 5, Entry 2)**. Upon isolation, obtained 60% yield. Changing the base from TEA to DIPEA resulted in trace formation of 36a **(Table 5, Entry 5)** (optimized condition has TEA). No formation of **36a** was observed when the base is a secondary amine DIPA **(Table 5, Entry 6)**. In order to check the effect of excess triethylamine on formation of **36a**, 20 equiv. of triethylamine was used in the reaction keeping other parameters of the optimization condition-2, reaction went for full conversion, with an isolated yield of 70% **(Table 5, Entry 4)**.

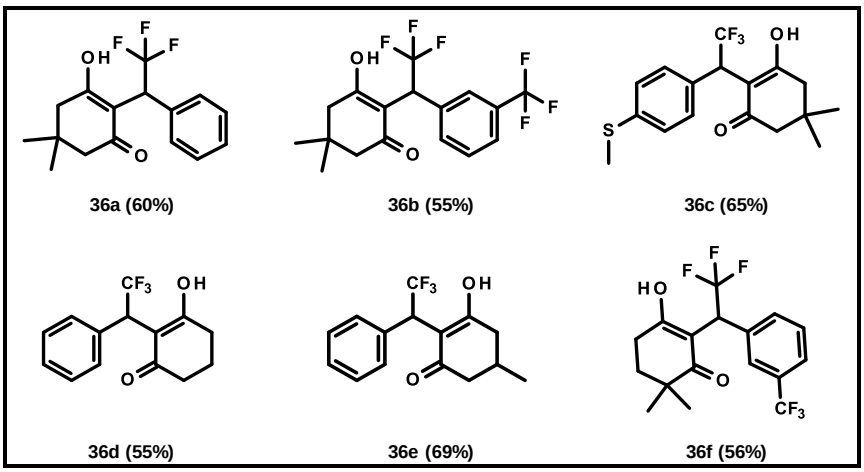


Figure 5: Substrate scope for reaction of different trifluoromethylated cyclic-enediones with triethylamine

To explore the substrate scope of the method, Cyclic enediones **(34)** were screened using optimized reaction condition to get desired compounds in 55–69% yield. Moderate yields were obtained in the case of **36a** (60%), **36b** (55%), **36d** (55%) and **36f** (56%) (**Figure 5**). A fairly decent isolated yield is observed for **36c** (65%) and **36e** (69%) (**Figure 7**).

3.2 Synthesis of fused 4*H*-Pyrans from trifluoromethylated cyclic-enediones.

In 2013 Kanakaraju *et.al*. reported a methodology to prepare 4*H*-pyrans using aldehyde, malononitrile and ammonium acetate.[42] This methodology inspired us to check the formation of CF_3-4*H* pyrans from **34** using the reported conditions. Initially, the reaction was tested with **34c**, which was treated with malononitrile and ammonium acetate in methanol at room temperature.

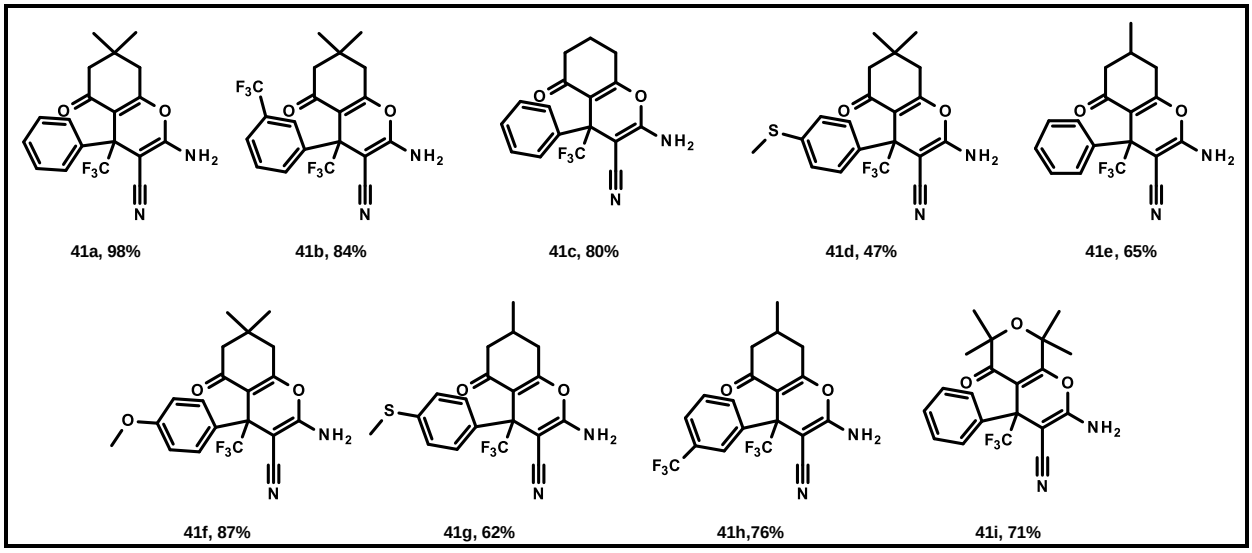
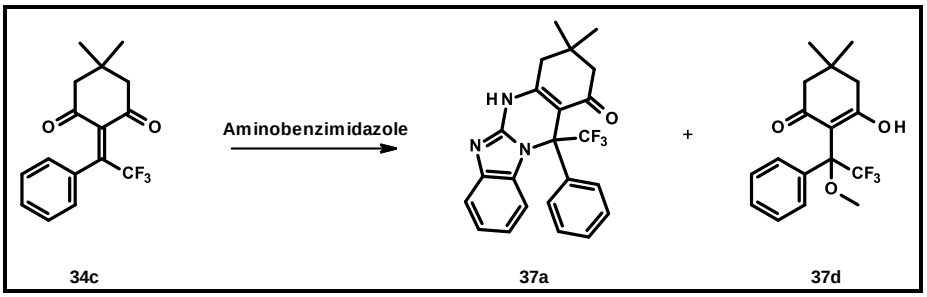


Figure 6: Substrate tolerance for synthesis of Fused 4*H*-Pyran derivatives

which was collected by filtration from the reaction mixture, where the product was found to be insoluble in 98% yield. Hence, the conditions were used to check the substrate scope with various trifluoromethylated cyclic-enediones (**34**) prepared earlier. Trifluoromethylated enediones **34c**, **34h**, **34a**, and **34r**, upon reaction with malononitrile, gave an excellent yields of **41a** (98%), **41b** (84%), **41c (80%), 41f** (87%) under-reported conditions, whereas **34m**, **34l**, **34b**, **34g** and **34e** gave the desired products **41d** (47%), **41g** (62%), **41e** (65%), **41h** (76%), and **41l** (71%) in moderate to good yield **(Figure 6)**.

3.3 Reaction of trifluoromethylated cyclic-enediones with aminobenzimidazole.



Scheme 1: Reaction of trifluoromethylated cyclic-enediones with aminobenzimidazole

In 2021, Fedtov *et. al*., reported the reaction of cyclic-enone with aminobenzimidazole to synthesise a fused heterocyclic compound, inspired by this protocol, we executed the reaction of **34c** with aminobenzimidazole using methanol as solvent at reflux temperature without any base. To our surprise, no desired product was obtained; however, an impurity was obtained in substantial quantity, which was isolated and characterized. The characterisation suggested that a β-attack by alcohol to **34c** was the primary reaction to give 3-hydroxy-5,5-dimethyl-2-(2,2,2-trifluoro-1-methoxy-1-phenyl-ethyl)cyclohex-2-en-1-one (**37e**). Attempts to access the title compound in DMF at 140 °C, as reported, also failed to yield the desired product.[43] This could be due to instability of the trifluoromethylated cyclic-enedione at elevated temperatures.

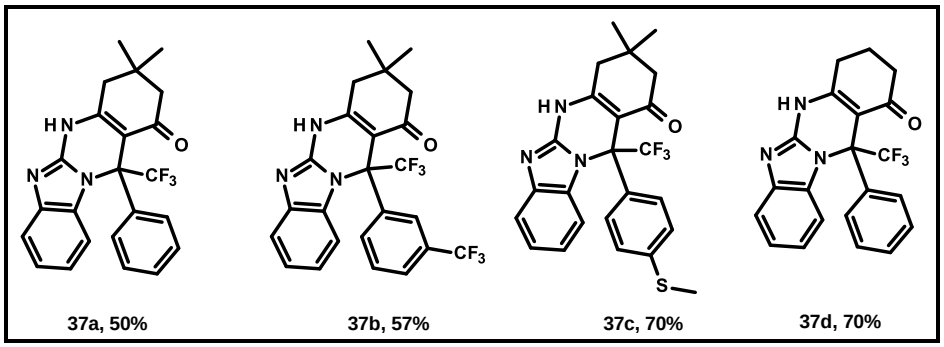


Figure 7:Reaction of trifluoromethylated cyclic-enediones with aminobenzimidazole

To our delight, when the **34c** was subjected to optimization condition-1 as reported earlier (**Table 4, Entry 4),** the desired product **37a** was observed by LCMS and the product obtained by filtration of the reaction mixture at RT in 50% yield. Further, the scope of reaction was studied by reacting **34h**, **34m** and **34a** with aminobenzimidazole to obtain **37b**, **37c** and **37d** in moderate to good yield (57–70 %).

3.3.1 Reaction of alcohols with trifluoromethylated cyclic-enediones.

To further understand the stability of **34c** in alcoholic solvents, **34c** was treated with methanol and ethanol. In alcoholic solvents, **34c** underwent Michael addition of alcohol at the β-position to give adduct.

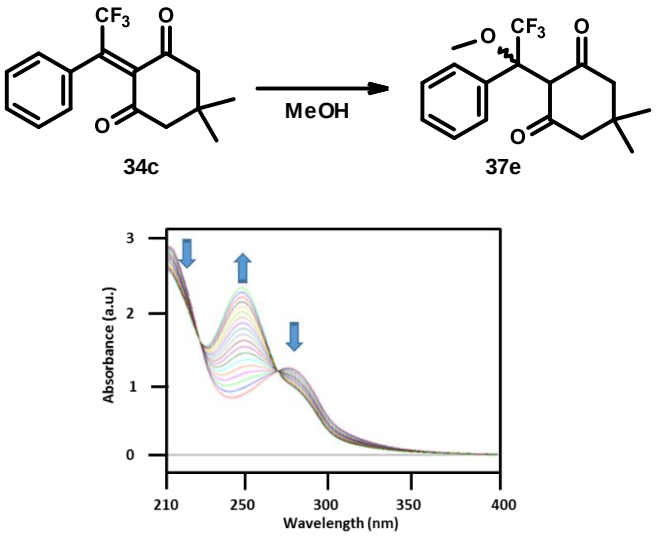


Figure 8: UV-Vis spectroscopic study to evaluate the stability of 34a in methanol

The reaction of **34c** with methanol was monitored by UV-Vis spectroscopy (**Figure 8**), and a clean transformation of **34c** (λ_{max} 280 nm, $t_{1/2}$: 5.1 h, methanol) to it Michael adduct (**37e**, (λ_{max} 253 nm) was observed with isosbestic points at 220 nm and 270 nm.

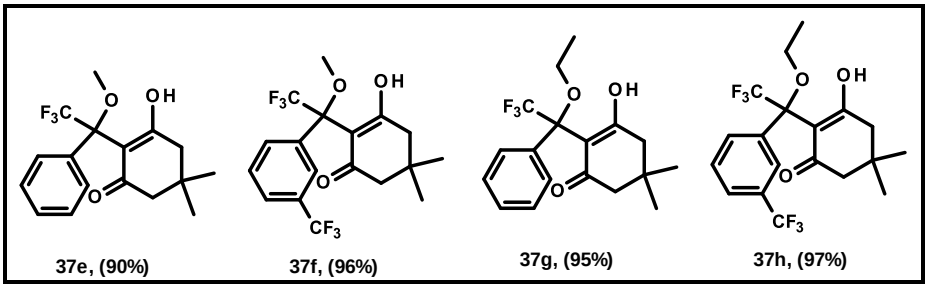


Figure 9: Adduct formation with different alcohols

Substrate tolerance for the adduct formation was checked for methanol and ethanol, and found to give a products with excellent yields (**Figure 9**), initially, reaction took 16h at RT, but when the reaction was carried at reflux temperature, the reaction was completed at 3–5 h. The reaction of hindered alcohols was found to be unreactive or slow hence, these substrates could be used in hindered protic and alcoholic solvents.

3.3 Biology.

All the molecules synthesised were tested for biological activity in three indications (i.e., insecticide, fungicide, and herbicide) of agrochemical interest.

1. 1,4-dihydropyrimidines: phenyl pyrimidine derivatives (**38a-f**) showed mild to moderate activity in fungicide indication at higher concentrations, while methyl (**35a-d**) and cyclopropyl derivatives (**39a**) showed poor to no activity in any of the indications.
2. 4*H*-pyrans: 4*H*-pyran derivatives (**41a-i**) showed moderate herbicidal activity at higher concentration.
3. Alcohol adducts: Methanol derivatives (**37e-f**) showed mild insecticidal (healthy leaf area) activity ethanol derivatives (**37g-h**) showed no activity in any of the indications.
4. 3-Hydroxycyclohex-2-en-1-ones: Reduced products (**36a-f**) Showed mild herbicidal activity at higher concentrations.

3.4 Summary and Conclusion.

The major finding of this chapter based on synthetic utility and biological evolution are as follows:

1. Application of novel trifluoromethylated cyclic-enediones for accessing CF_3 heterocycles with a quaternary chiral centre was demonstrated.
2. The structure of the compound was confirmed based on ^{1}H NMR, 2D NMR spectra, HRMS, and X-ray analysis.
3. All the molecules were tested for biological activity. Phenyl pyrimidine derivatives (**38a-f**) showed mild to moderate activity in fungicide indication at higher concentrations, 4*H*-pyran derivatives (**41a-i**) showed moderate herbicidal activity at higher concentrations, while the alcohol adducts(**37e-f**) and reduced products (**36a-f**) showed mild insecticidal and herbicidal activity respectively.

4. Chapter 4: Application of trifluoromethylated cyclic-enediones in the synthesis of 5-membered heterocycles.

5-membered heterocyclic compounds are interesting target compounds found in a wide range of drugs and have galvanized the interest of medicinal chemists worldwide.[44,45] 5-member heterocycles are classified as pyrazoles, imidazoles, oxadiazoles, tetrazoles, triazoles, thiadiazoles, and others depending on the nature, number, and arrangement of heteroatoms in them. They are important structural units in many pharmaceutical and agrochemical compounds. They can be found as an isolate or as fused rings (e.g., benzimidazole, benzisoxazole, etc.).

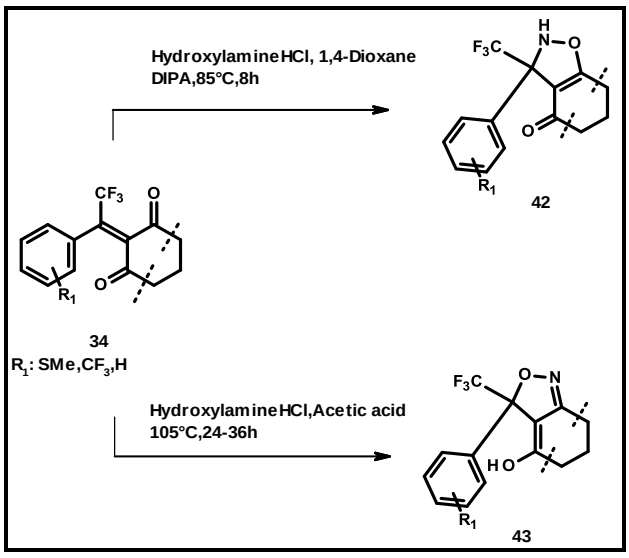
Several different methods are available for the synthesis of five-membered heterocyclic compounds using, namely Paal–Knorr pyrrole synthesis, Hantzsch Pyrrole Synthesis, Barton–Zard synthesis, Knorr pyrrole synthesis, Debus Synthesis, Radiszewski Synthesis, etc.

Inspired by the synthetic utility and application available in the literature, we investigated the application of trifluorinated cyclic-enediones (**34**) to access fused 5-membered trifluromethylated heterocyclic compounds. Current work outlines the synthesis of dihydroisoxazoles, 2,3-dihydrofurans and 4*H*-pyrazoles using hydroxylaminehydrochlorides, isocyanides and hydrazines as reagents, with cyclic enedione as a scaffold.

4.1 Synthesis of dihydroisoxazoles using trifluoromethylated cyclic-enediones.

In the current work, we successfully demonstrated the synthesis of fused substituted dihydroisoxazole and unsubstituted dihydroisoxazole using hydroxylaminehydrochlorides and cyclic enediones as scaffolds. [46,47]

Above optimised condition 1 (**Chapter 2, Table 4, entry 4**) used for the synthesis of 1,4-dihydropyrimidines were subjected to **34c** in the presence of hydroxylamine hydrochloride. The reaction mixture after workup gave the desired product **42a** in 71% yield, which was further characterised by 2D-NMR. The method was extended to different enediones and *N*-substituted hydroxylaminehydrochlorides to check the substrate scope of the reaction and able to synthesise compounds with moderate to good yield of 20–71%.



Scheme 2: Reaction of different enediones with hydroxylamine hydrochlorides to give regio-selective fused isoxazolines

Reaction of hydroxylamine hydrochloride with **34a**, **34h** and **34b** gave product with good yield **42a** (71%), **42b** (70%) and **42c** (69%), while the reaction with **34m** gave product **42d** moderate yield of 55%.

When the substrate **34c** was subjected to hydroxylamine hydrochloride using acetic acid as solvent at 105°C for 36 h, we observed another regiomer of **42c**, i.e., **43a**, wherein the nitrogen and oxygen position in the dihydroisoxazoline ring were interchanged.[48] The substrate scope

for this regio isomer was explored (**Figure 11**) for different cyclic-enediones to obtain **43a** (50%), **43b** (42%), **43c** (50%) and **43d** (53%). The yields were relatively low and could be attributed to instability of ene-dione to higher reaction temperatures for prolonged reaction time. Further, **43b** was characterized by X-ray crystallography **(Figure 10)**. The crystal structure indicates that the crystal of **43b** and Hydrogen bonding between the hydroxyl and nitrogen of the isoxazole rings of molecules in the crystal lattice.

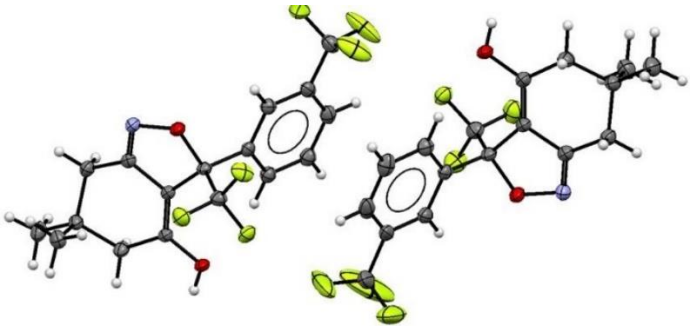


Figure 10: ORTEP structural representations of 43b

Interestingly, when the enedione **34m** was used as substrate, the reaction yielded only traces of the product, along with starting material, and several other impurities, such as aromatization due to the elimination of CF_3 and Dimedone as observed in LCMS

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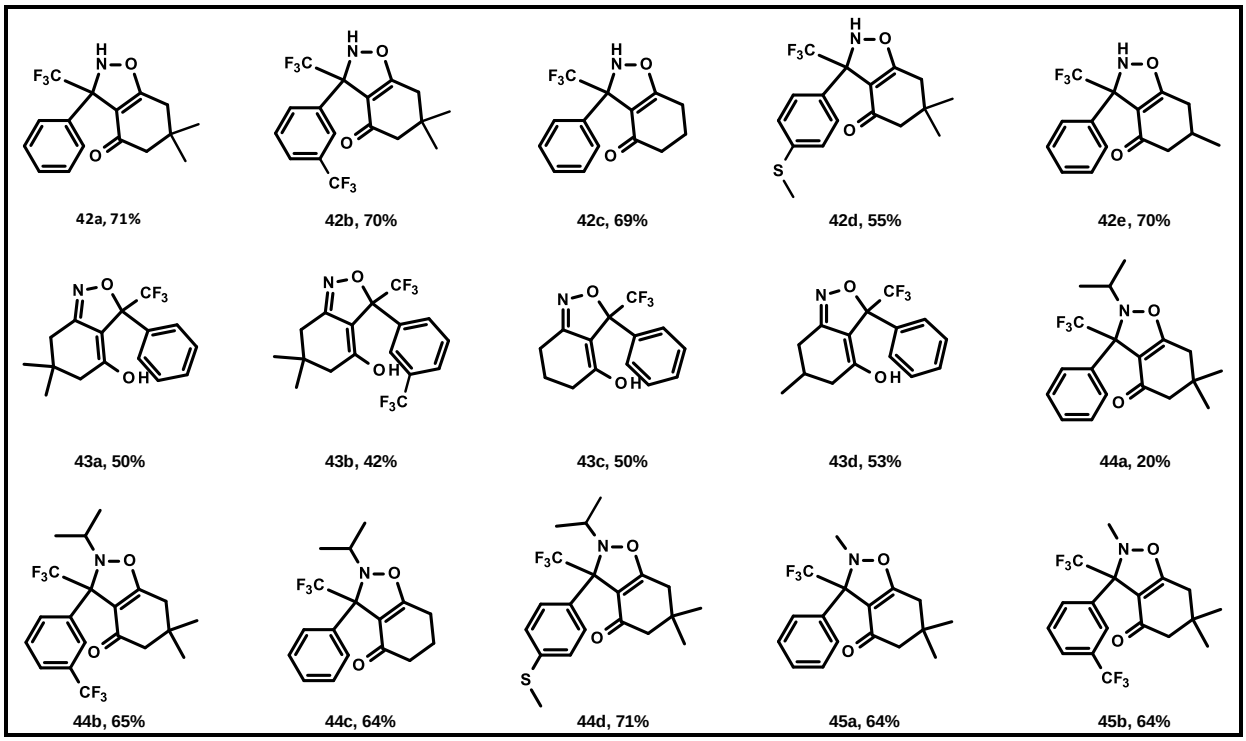


Figure 11: Substrate scope for the reaction of different enediones with hydroxylaminehydrochlorides.

The scope of reaction was further studied by reacting the trifluoromethylated cyclic-enediones with *N*-methylhydroxylamine hydrochloride and *N*-isopropylhydroxylamine hydrochloride using optimised protocol-1 (**Chapter 2, Table 4, entry 4**) to get corresponding products with moderate to good yield (**44b** (65%), **44c** (64%), **44d** (71%), **45a** (64%) and **45b** (64%) in **Figure 11**).

4.2 Synthesis of fused 2,3-dihydrofurans with a quaternary carbon with CF_3 group:

Fused and substituted furans are an important class of oxygenated heterocyclic compounds[49,50] and are the core components of several natural products exhibiting a wide range of therapeutic effects hence of high pharmacological importance.[51,52]

Motivated by the synthetic utility and application of our enediones, we tried to scope the synthesis of dihydrofurans. In the current work, we report the synthesis and characterization of fused 2,3-dihydrofurans **(46a-f, 47a-f, 48a-f)** by reacting isocyanides with the various trifluoromethylated enediones as a scaffold. As a model reaction, trifluoromethylated cyclic-enedione **(34)** and cyclohexyl isocyanide were stirred at ambient temperature in DCM as solvent. The reaction successfully gave the desired 3-(trifluoromethyl)-dihydrobenzofuran obtained in 88% yield. The product was confirmed by NMR and HRMS analysis.

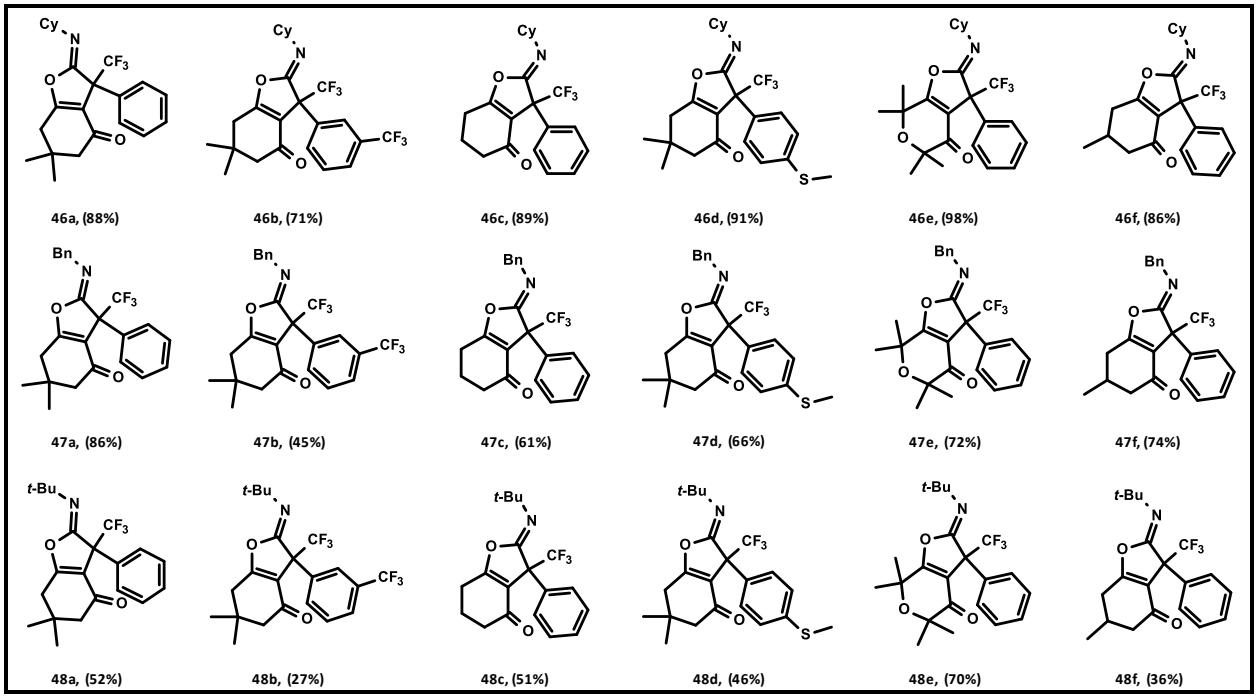


Figure 12: Substrate scope for the synthesis of 5,7-dihydrobenzofuran-4-one derivatives 46a-f,47a-f,48a-f, synthesised using different trifluoromethylated cyclic-enediones and isocyanide derivatives.

With this reaction condition, substrate tolerance was explored with different trifluoromethylated cyclic-enediones as well as different isocyanides to get low to excellent yield **(Figure 12)**.

When the isocyanide was varied from *t*-butyl isocyanide to benzyl isocyanides to cyclohexyl isocyanide, a significant increase in the yield was observed for each of the cyclic enediones.

Among the different isocyanides, *t*-butyl isocyanide showed comparatively lower yield might be due to bulky *t*-butyl group **(48b** (27%), **48f** (36%), **48d** (46%), **48c** (51%), **48a** (52%) and **48e** (70%)).

Whereas with different trifluoromethylated cyclic enediones, varied yields were obtained with each of the isocyanides. Trifluoromethylated cyclic enediones with *m*-CF_3 in the aromatic ring showed the lowest yield (**48b** (27%), **47b**(45%), **46b**(72%)), while the cyclic enedione with 2,2,6,6-tetramethyltetrahydropyran gave very good yield (**46e**(98%), **47e**(72%), **48e**(70%)). Other trifluoromethylated cyclic enediones gave moderate to good yield among the series.

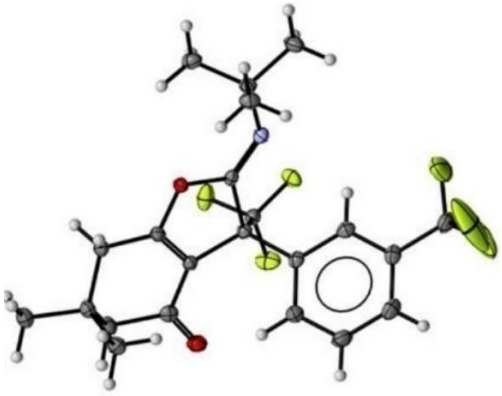


Figure 13: ORTEP structural representations of 48b

48b was further characterized by X-ray crystallography (**Figure 13**). The crystal structure indicates that 8 molecules pack together in the crystal unit cell. As anticipated, **48b** contains an equal ratio of enantiomers to form a racemic mixture.

4.3 Synthesis of fused 1*H*-pyrazole:

In the current work, we successfully demonstrated the synthesis of fused 1*H*-pyrazole using cyclic enediones as scaffolds. When the optimised protocol-1 (**Chapter 2, Table 4, entry 4**) was subjected to **34c** with phenyl hydrazine, the desired product was obtained along with an impurity which was formed as a result of the elimination of the CF_3 group driven by aromatization.[53] However, when the reaction temperature was reduced to 20–25°C, the desired product **49a** was obtained in 71% yield (**Figure 14**). Substrate tolerance were studied with different enediones to achieve moderate to good yield (**49a** (70%), **49b** (74%), **49c** (64%), **49d** (60%)). When the pyrimidine hydrazine was used as a reagent, yields (**49e** (72%), **49f** (80%), **and 49g** (70%)) were higher compared to respective products from the phenylhydrazine derivatives.

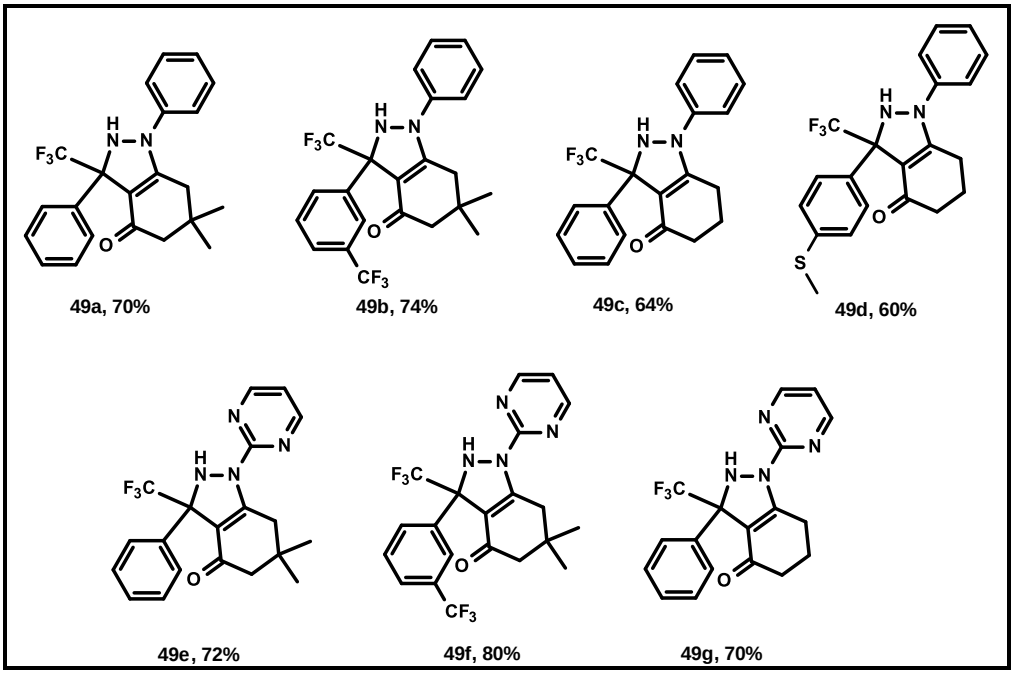


Figure 14: Substrate scope for hydrazine derivatives

The presence of the electron withdrawing group at the aromatic ring of trifluoromethylated cyclic-enediones gave a good yield (**49b** (74%), **49f** (80%)), while the donating group in the aromatic ring resulted in a moderate yield of the desired product (**49d** (60%)). All the fused 1*H*-pyrazole derivatives (**49**) synthesised were tested for biological activity.

4.4 Biology.

All the molecules synthesised were tested for biological activity in three indications (i.e., insecticide, fungicide and herbicide) of agrochemical interest.

1. 2,3-dihydroisoxazoles: 2,3-dihydroisoxazoles (**42a-e**) showed mild insecticidal and herbicidal activity. 4,5-dihydroisoxazole (**43a-d**) showed moderate to good fungicidal activity. N-substituted 2,3-isoxazoles(**44a-d,45a-b**) showed moderate insecticidal activity.
2. 2,3-dihydrofurans: 2,3-dihydrofuran derivatives (**46a-f,47a-f,48a-f**) showed no activity in any of the indications.
3. 1*H*-pyrazole: Pyrimidine pyrazole derivatives (**49e-g**) showed moderate to good insecticidal activity, whereas phenyl derivatives (**49a-d**) showed no activity in any of the indications.

4.5 Summary and Conclusion.

The major finding of this chapter based on synthetic utility and biological evolution are as follows:

1. Demonstrated application of trifluoromethylated cyclic-enediones in the synthesis of 5-membered heterocycles. The structure of the compound was predicted and confirmed based on ^{1}H NMR, 2D NMR spectra, and HRMS and further confirmed by X-ray analysis.
2. All the molecules were tested for biological activity, Pyrimidine pyrazole derivatives (**49e-g**) showed moderate to good insecticidal activity and 4,5-dihydroisoxazole (**43a-d**) showed moderate to good fungicidal activity.

5. Chapter 5: Synthesis of mono-charged Pyrazines and pyridines to check their potential as agrochemical lead compounds

Mono-charged Nitrogen Heterocycles or quaternary Ammonium compounds, also generally known as QACs or Quats, are a diverse family of polyatomic ions possessing a positive charge and a negative counter-charged ion. The structure of Quaternary ammonium compounds consists of a positively charged nitrogen atom with four or three substituents and one double bond. The core quaternary ammonium compound can contain one, two, or multiple charged nitrogen atoms, including those in heterocyclic compounds (Pyrazine, piperidine, pyridine, imidazole, etc.). In the case of bis-QACs, multi-QACs, and poly-QACs, the structure that connects the charged nitrogen atoms (the head) is called a spacer or linker, and the alkyl chains extending from the heads are called tails.

The first studies of QACs as antibacterial agents were carried out at the beginning of the last century. With the discovery of benzalkonium chloride (BAC) in 1935, QACs found application in medical practice. Subsequently, the study of this class of compounds has led to the discovery of many valuable properties of QACs, due to which they are now used as surfactants, personal hygiene products, cosmetics, softeners, dyes, biological dyes, and, of course, antiseptics and disinfectants with a wide spectrum of action. [54]

In the last few decades, quaternary ammonium compounds have been included in most antiseptics and disinfectants and used in various areas, from household and agriculture to medicine and industry. These are widely used as herbicides, antimicrobials, cleaners, sanitizing agents, phase transfer catalysts, and also asymmetric synthesis in chemical reactions.[55]

Among the widely used charged heterocyclic compounds, the most popular ones are Paraquat and Diquat (**Figure 15**), which are used as non-selective herbicides in the world. Both are di-charged compounds, methylated at nitrogen as quaternary centres.[56] However, compounds are known to be toxic[57] due to their methylating property, because of which the molecules are facing regulatory issues in most of the world markets.[58]

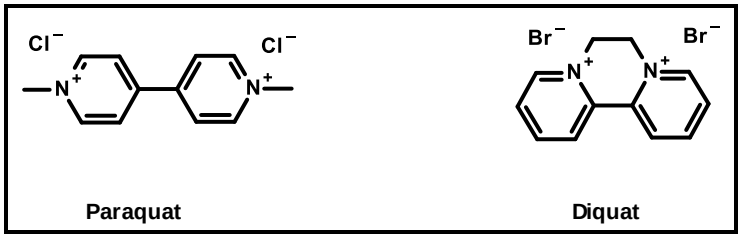


Figure 15: Non-selective herbicides derived from pyridine derivatives

Thus, our work started with the hypothesis that the synthesis of mono-charged compounds of pyrazine with a directed-hydrogen bond donor would reduce the toxicity and also the oxidising power thereby enhancing stability.[59] Mono-charged molecule synthesis was planned by blocking one side of the molecule either with oximes or phenols (as donors of hydrogen bond) so that we get targeted alkylation at the other end. These oximes or phenols are carefully chosen based upon literature survey showed them to influence herbicidal activity and are used as therapeutic agents.[60,61]

5.1 Preparation of charged pyrazine derivatives

The synthetic plan was to develop a convergent approach to access various pyrazine derivatives *via* the use of coupling[62] chemistry, such as Suzuki coupling,[63] Sonagashira coupling,[64] Suzuki-mayura coupling[65] etc., starting from di-halo pyrazine derivatives followed by a divergent approach to quaternary-hydrogen bonded salts.

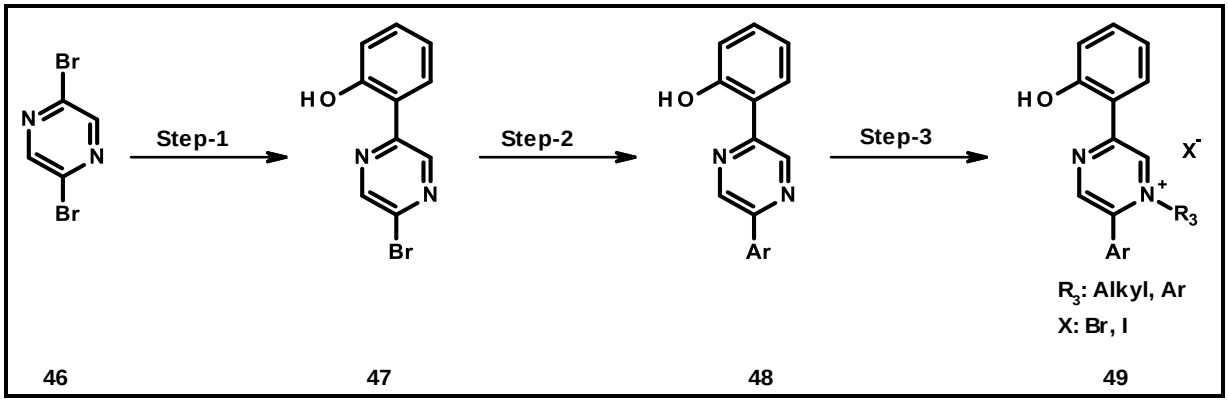
The work plan would include the following.

1. Substitution with various R_1-R_4 to screen for electron withdrawing and electron donating groups either *via* the cross-coupling methods or using the linear synthesis starting from α-dicarbonyl and *o*-diamines.

2. To include R_5 with different alkyl/aryl halides to give diverse charged species and their biological evaluation.

5.1.1 Preparation of charged tri-aryl pyrazinium compounds.

As per the hypothesis, the synthesis of mono-charged pyrazine derivatives of bi-aryls and tri-aryls were prepared. Biphenyls and triphenyls can be prepared using various coupling reactions. The detailed literature survey revealed that among the various coupling reactions, Suzuki coupling[66] (**Scheme 3**) was most suitable to access biphenyls of our interest.
In order to test our hypothesis, we planned to synthesise 2-aryl-5-bromo pyrazine derivative (**47**) and triaryl systems **(48)** using Suzuki coupling as shown in Scheme. The product **47** was isolated by coupling dibromo pyrazine (**46**) with corresponding aryl boronic acid in 70% yield. Product **47** was subjected to a second Suzuki coupling with different aryl boronic acid, resulted in the formation of product **48** with up to 60% yield.



Scheme 3: Mono-charged pyrazinium salts from dibromo pyrazine.

5 different triaryl systems (**48 a-e**) were synthesised and purified by column chromatography, and the pure compounds were characterized by ^{1}H, ^{13}C NMR, HR-MS and IR spectroscopy.

Having obtained the triaryls and Bi-aryls, we explored the synthesis of monocharged compounds of the same directed by H-bond with the anticipation that the alkylation would occur at the nitrogen not involved in a hydrogen bond. A model reaction was carried out between 2-aryl-5-bromo pyrazine derivative (**47**) with methyl iodide. No desired product was obtained with the reaction either at RT or at reflux temperature, this could be due to partial charge formation on the ring due to hydrogen bonding.

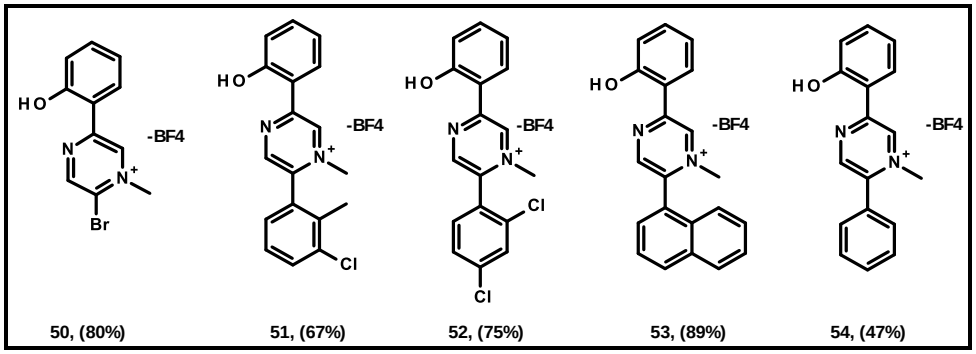


Figure 16: Mono-charged pyrazinium salts using bi- and tri-aryl compounds change compound numbers

Methylation using strong methylating agents such as dimethyl sulphate in 1,4-dioxane as solvent reactions were also unsuccessful both at room temperature as well as elevated temperature. After much of the unsuccessful attempts at salt formation at the pyrazine, alkylation was carried out using trimethyloxonium tetrafluoroborate at room temperature using dichloromethane as solvent. To our delight desired alkylated product **50** was obtained in 80% yield (**Figure 16**). The structure of the product was confirmed by 2D NMR analysis. ^{1}HNMR showed (**Figure 17**) a methyl group attached to quaternary nitrogen at δ 4.41 for compound **50**.

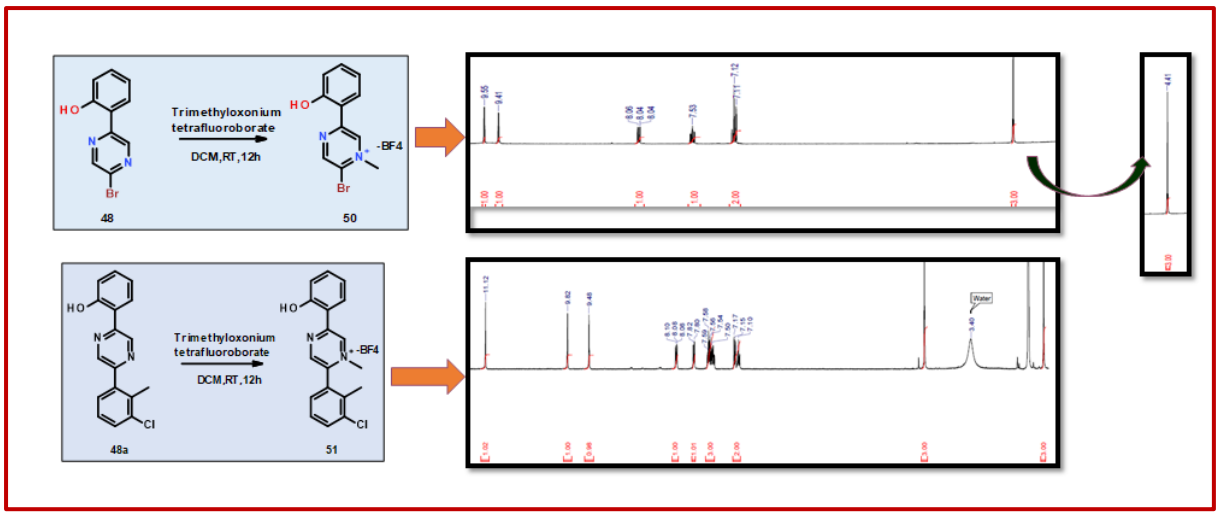
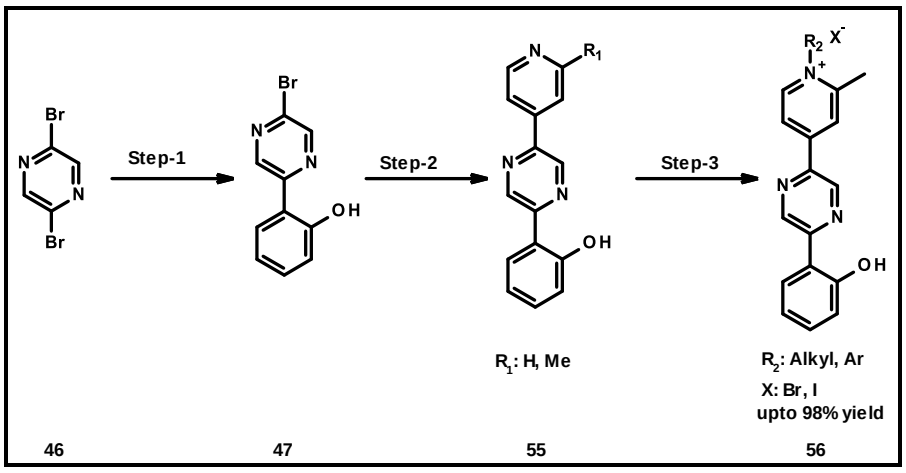


Figure 17: ^{1}HNMR representing formation of methyl salts of 48 and 48a using trimethyloxonium tetrafluoroborate

Further, all the triaryls were subjected to alkylation using trimethyl oxonium tetrafluoroborate to give products with moderate to good yield (**51** (67%), **52** (75%), **53** (89%), **54** (47%)). All the molecules were tested for biology.

5.1.2 Preparation of charged tri-aryl pyridinium compounds.

Product **47** was subjected to a second Suzuki coupling with different pyridyl boronic acid, resulted in the formation of product **55** with up to 45% yield.



Scheme 4: Mono-charged pyridinium salts from dibromopyrazine

When the triaryls with pyridine were subjected to reflux with methyl iodide, it readily formed salt at pyridine nitrogen and not at the pyrazine nitrogen as expected. The reaction was carried out using ethyl iodide, allyl bromide and bromoacetic acid to give respective pyridinium salts of the triaryls. Excellent yields were obtained (**Figure 18**) with methyl, ethyl, and allyl halides (**56d** (98%), **56c** (89%), **56f** (77%)), whereas reaction with bromoacetic acid gave poor yield (**56e** (34%) due to lower conversion even after longer hours of reaction. Alkylation was also

successfully demonstrated on triaryls containing substituted pyridines in moderate yield (**56a** (63%), **56b** (56%), **56g** (66%).

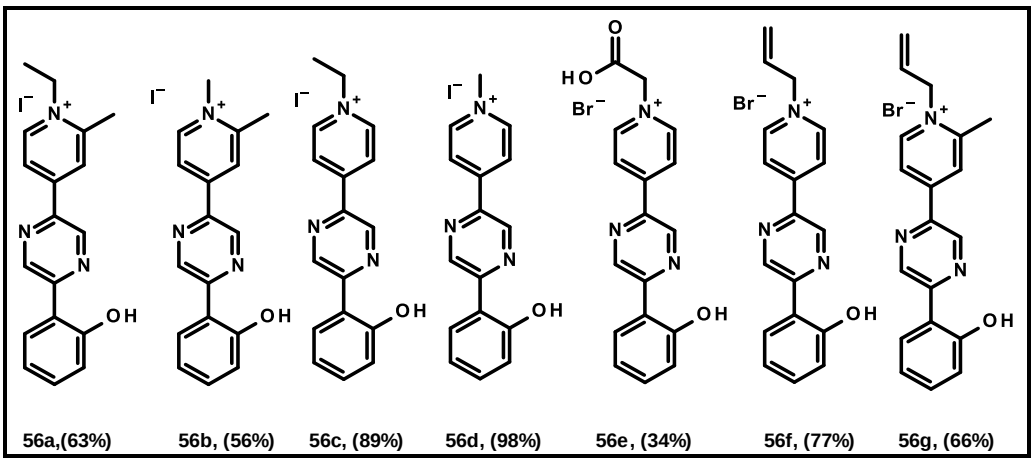
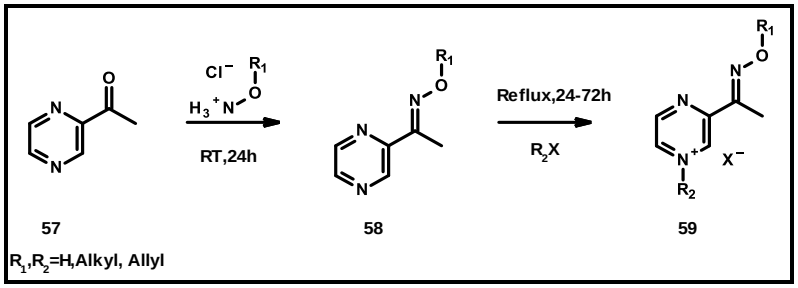


Figure 18: Mono-charged pyridinium salts

5.1.2 Preparation of mono-charged simple pyrizinium compounds.



Scheme 5: Mono-charged pyrazinium salts using 2-acetylpyrazine

After completing the synthesis and biological evaluation of triaryl salts (**56**) we shifted our focus to synthesis of simple mono-charged pyrizinium compounds with oxime handle, as shown in **Scheme 5**. The reaction of 1-pyrazin-2-ylethanone with hydroxylamine hydrochloride in methanol gave 71% of **58a**. The reaction of 1-pyrazin-2-ylethanone with N-methyl hydroxylamine hydrochloride and *O*-allyl hydroxylamine hydrochloride to give **58b** (42%) and **58c** (17%), respectively. Yields were comparatively lower due to the loss of product during the distillation.

Having the pyrazine oxime scaffold in hand, we explored the synthesis of pyrazinium salts by reacting the same with a variety of alkyl, allyl and phenacyl halides to obtain an array of mono-charged pyrazinium salts (**Figure 19**). Reaction with methyl iodide gave **58a** in 83% of **59a** and 79% (**59b**) with ethyl iodide. However, as the length of the alkyl chain of the alkyl halide increased, reaction conversion was poor and thus yields dropped *n*-pentyl halide and *n*-heptyl halide where used (**59c** & **59d**, **Figure 19**). Reaction with allyl bromide gave the product (**59e**)

with a moderate yield of 53%, whereas reaction with bromoethanol gave the product (**59f**) with a lower yield of 32%.

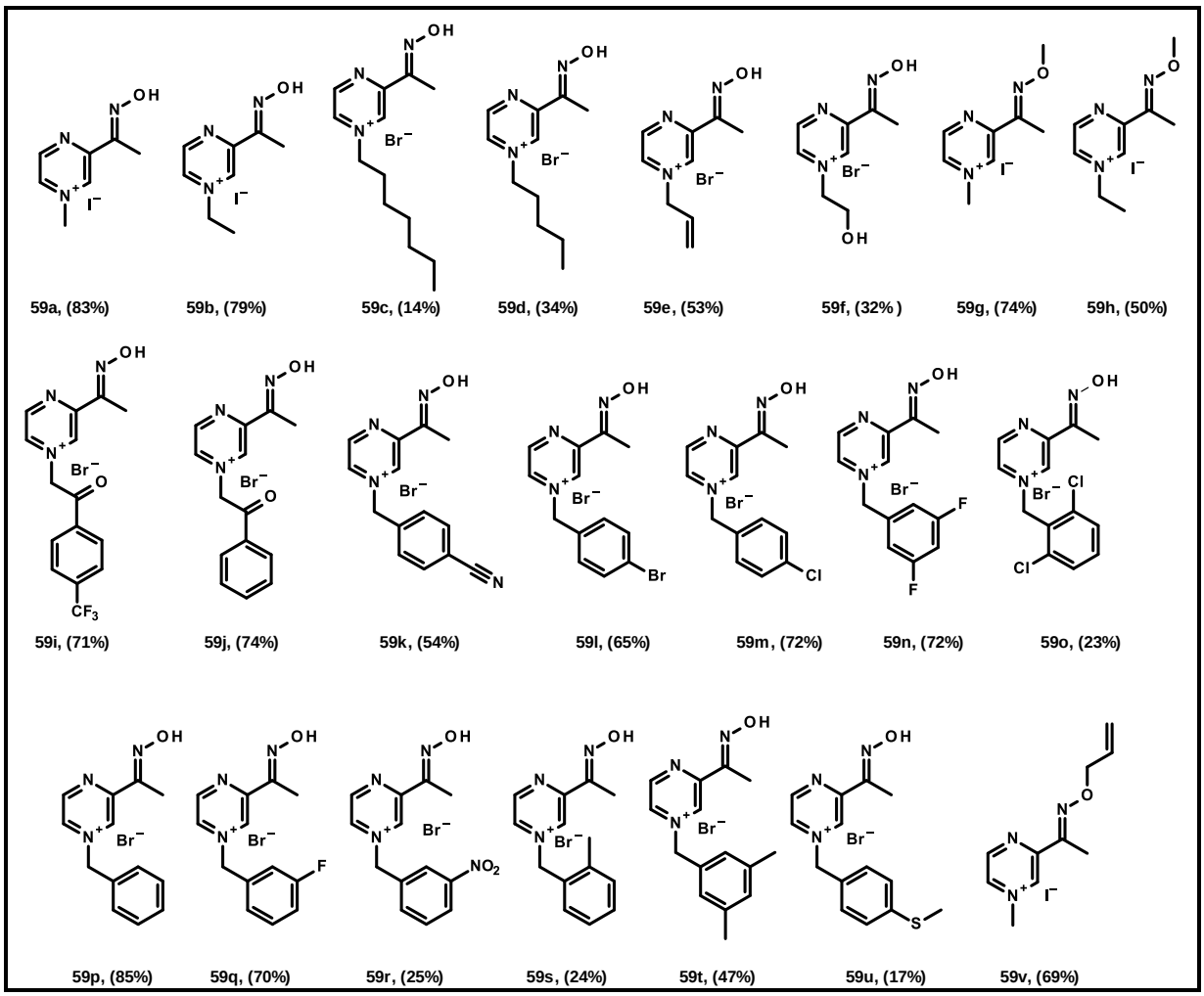


Figure 19: Simple mono-charged pyrazinium compounds

Further, **58a** was subjected to alkylation using phenacyl bromide and *p*-trifluoromethyl phenacyl bromide to get product **59j** (74%) and **59i** (71%), respectively. When the reaction was done with benzyl bromide, the product **59p** obtained 85% yield, while the substituted benzyl bromides gave 23–72% yield (**59k-59o**, **59q-59u**).

Among the substituted benzyl bromides, *p*- and *m*- halo substituted benzyl bromides gave good yield (**59q** (70%), **59l** (65%), **59m** (72%), **59n** (72%)). 4-*S*-methyl, *m*-nitro and *p*-cyanobenzyl bromides gave poor to moderate yields (**59u** (17%), **59r** (25%) and **59k** (54%)). 2-methyl benzyl bromide and 2,6-dichlorobenzyl bromide gave poor yield (**59s** (24%)) and (**59o** (23%), respectively could be due to steric factors influencing the salt formation.

When **58b** was refluxed with methyl iodide desired methylated product **59g** was obtained in 74% yield, while the refluxing with ethyl iodide gave slightly lesser yield (**59u** (50%)) as

expected due to increase in the alkyl chain length. While the reaction of **58c** with methyl iodide gave 69% of the desired product **59v**.

5.2 Biology.

All the molecules synthesised were tested for biological activity in three indications (i.e., insecticide, fungicide, and herbicide) of agrochemical interest.

1. Bi- and Tri-aryl pyrazinium compounds: Dichloropyrazinium tetrafluroborate derivative **52** showed good herbicidal activity, and bi-aryl derivative **50** showed mild fungicidal activity.
2. Tri-aryl pyridinium compounds: 2-methylpyridinium iodide derivatives **56a** and **56b** showed good fungicidal activity.
3. Simple pyrazinium compounds: Simple pyrazinium salts showed no activity across any indication.

5.3 Summary and Conclusion.

The major finding of this chapter based on synthetic utility and biological evolution are as follows:

1. Synthesis of monocharged pyrazine and pyridine derivatives with diverse substitution pattern has been demonstrated. The structure of the compound was confirmed based on ^{1}H NMR, 2D NMR spectra, and HRMS.
2. The compounds have been tested in the agrochemical field to test their potential as fungicides, insecticides, and herbicides. Dichloropyrazinium tetrafluoroborate derivative **52** showed good herbicidal activity, and bi-aryl derivative **50** showed mild fungicidal activity. 2-methylpyridinium iodide derivatives **56a** and **56b** showed good fungicidal activity.

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LIST OF RESEARCH PUBLICATIONS

1. National/International Journals.

   - ✓ Published a paper entitled “Synthesis of novel 2-(2,2,2-trifluoro-1-aryl-ethylidene)cyclohexane-1,3-dione: Scaffolds for reagent-based diversity-oriented synthesis” **Mahesh R. Kalbagh**, Damodar Karuturi, Shashidhara Kulala, Mark Montgomery, Prashantha Kamath, Mukul Lal, *Synth. Commun.*, **2020**, *50*, NO. 20, 3062–3071.

2. National/International Conference Proceedings.

   - ✓ A poster titled “Reagent-Based Diversity-Oriented Synthesis Approach to Fused 1,4-Dihydropyrimidines, Dihydroisoxazolines, 2,3-Dihydrofurans, Substituted 4*H*-pyran and Cyclohexane-1,3-diones from 2-(2,2,2-trifluoro-1-aryl-ethylidene)cyclohexane-1,3-diones as Scaffold” is presented ICFAST-2022 in HCU Hyderabad with Poster No. CO-13. **Mahesh R. Kalbagh**, Damodar Karuturi, Mark Montgomery, Prashantha Kamath, Mukul Lal.

   - ✓ A poster titled “Synthesis of Novel *β*-Trifluoromethyl *β*, *β*-disusbstituted-1,3-cylcohexane-diones: Scaffolds / Dipoloarphiles for Reagent-Based Diversity Oriented Synthesis.” has been presented in the symposium “Sustainable chemistry and technology” conducted by Syngenta Biosciences on 4th November 2019. **Mahesh R. Kalbagh**, Damodar Karuturi, Shashidhara Kulala, Mark Montgomery, Prashantha Kamath, Mukul Lal.

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